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TRANSCRIPT

Medical Countermeasure Roundtable

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DR. GUTMANN: Thank you all for giving us such stimulating presentations. And this is an opportunity for us to pick your brains one more time, and it's become a tradition to begin with a question of asking you to pinpoint one single issue that you think is most important, but I want to refine that question somewhat in light of your excellent presentations.

We have been charged with a very specific charge on whether we recommend testing children for countermeasures such as anthrax vaccine, and we will do something broader than that as well. We will also develop a framework, and refine the framework that was given by the National Commission, now decades ago, for consideration of testing countermeasures on children.

So the question I'd like to ask you is, give us either what facts you think we need to take into account in order to reach our conclusion, or the ethical consideration that you think is most challenging, that we need to take into account. Rather than the single issue, because issue is very vague, so I want to say either what is the relevant fact or facts that you think are most important here, either that we know or that we need to know, or what is the relevant ethical concern that you think is most challenging, that we need to take into account? And, good. I have a volunteer.

DR. MOORE: I --

DR. GUTMANN: And we're going to go right down the line, and then we're going to open it up to Commission members. And this is meant to be brief, obviously.

DR. MOORE: Sure, I will be.

DR. GUTMANN: Thanks.

DR. MOORE: The two issues that I see are, how do you prepare for an attack that you don't know will ever come -- and this begs the point which was made earlier, which is how can you give a

vaccine, even with an infinitesimally small risk of morbidity, to guard against an event that may never occur? Therein lies the ethical dilemma, which I will leave to the ethicists.

However, having said that, if one assumes that the trial would go forward, where you're going to give the anthrax vaccine to children, how best to recruit? There are issues with protection of those children, of course, and again I'll defer that to the ethicists and the protocol writers, but how best to recruit patients and enroll subjects for this study?

I think you'd probably be best served by trying to enroll children of the military, that is, individuals who have already received the vaccine, and who believe in its effectiveness and its safety. You're more likely to, I think, have a successful enrollment in that regard.

The other is trying to vaccinate individuals who live in an anthrax -- if it were acceptable to say this -- an anthrax-endemic area. So for example, the Dakotas, my home state of Kansas, places where anthrax has, rarely, occurred, in Texas and other places where cattle are raised.

DR. GUTMANN: Thank you. Dr. Gorman?

DR. GORMAN: I think the children do need special ethical considerations and protections, and I think children also have a right, and responsible parents have a right, to make sure that their treatment, their therapeutics and vaccinations, are based on an equal knowledge basis with the decisions we make on adults.

DR. GUTMANN: Good. Thank you.

DR. THOMPSON: I'm not really sure that I have a lot to add on your narrow question, but as you broaden the discussion I think the thing that I would want to get before you is that, when you think about medical countermeasures, some of the things that would be regarded as least controversial and intrusive

-- and I'm thinking about information reporting and monitoring type activities -- are precisely the things that could have some of the largest impact on very small, very poor producers in other parts of the world.

DR. GUTMANN: Okay. Dr. Wendler?

DR. WENDLER: I would say three things. Knowing as much as you can about the risks of the vaccine, one. Two is knowing what the potential benefits of doing the study are, and in particular what you guys have been doing, thinking about that in the context of what the alternative designs are. So doing it pre-event, as people were saying, versus after the event.

And the third one was just mentioned, which is subject selection and figuring out the right way to do that. The military makes sense to me. I mean, I don't know much about the military. I've never been in the military. On the one hand, it makes sense to me. On the other hand, you might worry, since you don't know exactly to what extent soldiers can say no, and you want them in this context to be able to say no, both for themselves and for their kids.

DR. GUTMANN: Dr. Berkelman?

DR. BERKELMAN: I think the take-home that I want to drive home is the issue that zero data and limited data are very different. In terms of this issue of the framework, the threat with countermeasures has to be considered substantial, and it would seem that you would not want to be testing children if the threat is not either a high mortality or long-term disability. You saw tularemia, for example. You have to factor that in.

Whether there's an ability to get the needed data at the time of the event, and the ethical consideration may change as you gather more data. You will know much more about -- are you talking minimal risk? Are you talking more-than-minimal risk? -- as you gain more data, if you're going with older children down to younger children, for example. I think the subject selection is a huge issue.

DR. GUTMANN: Dr. Halsey?

DR. HALSEY: In terms of trying to help you with your framework, I think each potential agent and countermeasure needs to be assessed for whether or not there is a need for pre-exposure studies, such as immunogenicity of a vaccine.

I'm not sure that there's a uniform answer you can give to all of them, but each one should be scored. Maybe a scale could be developed with regard to the need. And some studies definitely need to be done post-exposure, to get large-scale safety data. So those protocols do need to be prepared.

The studies done pre-exposure should be in a manner that exposes the minimum number of children that's necessary, and the lowest risk possible situation, such as choosing the safest third-generation smallpox vaccine, if that's studied.

They should be tested in an area where there is some risk, and that will involve with regard to environmental exposures or potential exposure from a parent who's working with the agent, or perhaps the military, as we discussed earlier.

And I can't read my writing for the last note.

DR. GUTMANN: Well, you've satisfied the charge. You don't have to do everything. You can quit while you're ahead. That was very good.

DR. HALSEY: I'll quit now, I think.

DR. GUTMANN: You'll have another opportunity, I'm sure. Dr. Resnik?

DR. RESNIK: For me, the main issue would be, what is the benefit of the research? The social benefit. There should be some factual questions, like "What is the probability of a terrorist attack using this agent? How extensive would the attack be, even if they pulled one off? How much effect on the population would it have? Would a vaccine be at all helpful in dealing with this effect, or something else?"

And finally, "Would there even be an adequate public health response in place if all this were lined up?" Because we know with the Cipro attacks, the anthrax attacks in 2001, there was not an adequate supply of Cipro. So what's the point of doing all this research if we're not going to have an adequate supply of a vaccine, even if we have the research in place?

DR. GUTMANN: Thank you for that last comment, because that does suggest a very important human institutional factor that goes beyond what the science can give, but what the government actually does to prepare. That's very helpful.

I am open, and I see Barbara Atkinson has a question or comment.

DR. ATKINSON: I'm interested in whether, to the very specific question, what your opinions would be if you have one, on whether we really should recommend a small dosing study for anthrax specifically for children?

I mean, that's sort of the root of the simplest kind of question, and I just want to know if you have -- it's the bottom line. If you have an opinion or don't have an opinion, and why, if you do.

DR. RESNIK: I'll step in there and say no, because I don't think the benefit has been articulated clearly enough for society of doing this research. It might even be that, for a more dangerous, infectious agent, like H1N1 or something else, where vaccine development would be more appropriate. But I just don't see anthrax, at least, as being this kind of thing where it would be rapidly spreading through the population and killing off thousands of people before we could do anything, whereas a vaccine would be needed to deal with something like that.

DR. HALSEY: I'll give the opposite answer, in that I think yes, for a number of reasons.

One, I think the anthrax vaccine is relatively safe based upon the studies in adults. Second, I think it has been proven that anthrax would be an excellent bioterrorism agent, and perhaps one of

the more likely ones to be used in another setting. And there's a lot of public fear about it, which would enhance its desirability from the standpoint of a terrorist using it. And third, I think that it is feasible to do it in children whose parents have received the vaccine, as we've discussed, and there is at least a theoretical potential risk for the child themselves in the different settings we've talked about, endemic areas as well as the children.

So it's doable, and it wouldn't require very many children to get the vaccine to do the immunogenicity studies. You have to be realistic and acknowledge it won't provide the large-scale safety data that you would like to have. And that's what you have to say, because in order to do that you would have to study thousands, and I don't believe that's justified.

DR. GUTMANN: I have Steve on the list next. Oh, we're going down, I'm sorry. Go down the line.

DR. BERKELMAN: I'm next in line, I guess. And it's a difficult one. People are on teeter-totters sometimes, and I think probably going different directions. I would say yes, I do not believe you can get the immunogenicity studies you need, this needed data to be able to use a countermeasure, and believe that anthrax does pose a major threat to society. It could be delivered in major releases, both in time and in space, and would create widespread panic. And the panic is also a major issue to deal with. But it can produce widespread mortality.

DR. WENDLER: I don't know. I think you guys are going about it the right way. I think you need to ask the experts who can give you all the information we have on what the risks would be of those studies, what the alternatives are of doing them, what information you'd get out of that. And these are the people who can answer those questions. I don't know.

DR. THOMPSON: I guess I wouldn't venture a straightforward opinion to the question. I would not endorse the idea that there would be any particular benefit to rural populations to such a study, if that were an inference that was made. However, I might think that people who work on cattle ranches, and particularly actually bison ranches, might have a better understanding of what anthrax is and what it's about, and might actually be, for that reason, a population that would be worth exploring as a possible test bed.

DR. GORMAN: I would also say yes. In the event of another anthrax attack, this will be distributed to children under some mechanism. I would like to be able to tell the parents that I will be giving it to that I have some information that it works. I will not be able to tell them much about safety, but I would like to tell them that, in the dose I'm using, it works as well as it does in adults.

DR. MOORE: I don't share the view that it's a significant threat to the United States, but it certainly has been a threat, and I don't know whether it wouldn't be a threat in the future. But this is just my opinion.

With that in mind, I think it's reasonable to pursue the immunogenicity studies in children for two reasons. One is that the vaccine does, in fact, appear to be safe in adults, given the number of people that have received it. The other is, of the vaccines that are now available as countermeasures, this seems to be the safest. That is, it's not a live vaccine, and we have actual data showing its safety and immunogenicity. So if you're going to do something as a pilot study, this really -- I mean, in that term, this really would be the best agent to choose.

DR. GUTMANN: Thank you. Steve?

DR. HAUSER: Well, my question may have been partly answered by Dr. Gorman, but I might just revisit this issue that, in an earlier meeting of our Commission, was raised as an unattractive but

possible option, to deploy the appropriate anti-anthrax regimen in children, antibiotics and perhaps vaccine, based upon best available data and pre-clinical information.

And I just was trying to understand how feasible that option might be. How feasible it would be to deploy a regimen that would involve children in the case of an emergency without clinical data in children, that we would generate through the kinds of studies we're speaking about. Guessing on the dose.

DR. HALSEY: That's really where we're at right now. That's exactly what would happen this week if there were widespread exposures, you know, right now. The key decisionmakers would have to decide whether or not to do that, and they probably already have at least a tentative plan. And they're going to have to do that with whatever the next event is, assuming there will be another event. I mean, it almost has to be done. You have to have preparedness. So to recommend they do that is going to be reinforcing what, I think, all the key decisionmakers at the heads of the agencies involved already know.

DR. GUTMANN: Raju?

DR. KUCHERLAPATI: I have a question as to whether history provides us with any information about this. As all of you know, for the longest period of time, drug development never really involved children, and they were excluded from studies, and all of the decisions about the drug approval were really based upon adult studies. And when pediatricians really had to make a decision about the possible use of that, they just had to make a guess about whether it's appropriate for children, and what's the dose at which it would be appropriate for children.

And as a result of that, clearly, that has not benefitted children. And now, clearly, it has shifted now into -- now many people will argue that it is important to actually test the children for the right doses, and to be able to provide the right type of treatment.

Would that be applicable in thinking about this problem?

DR. HALSEY: I think you would benefit by having somebody from the FDA who was responsible for development and implementation of the pediatric rule, which I stated or paraphrased in my slide. And there was clear evidence in history that the pediatricians and other primary care individuals will use products that are available in children that have not been tested in children. They will use them if they believe that it is in the best interest of the child and the best available intervention that would be available. That is the responsibility of the caring physician. It will be done. I've done it. And I'm sure Dr. Gorman has done it, and others have done it.

And that has led to problems, because there have been adverse effects from some of these interventions that were not anticipated, because they hadn't been adequately studied in children. So I think that's an important part of history, that you could get more and you could approach the FDA. And there are some summary things that were written about this.

DR. GORMAN: If I can follow up, Diane Murphy, who is in charge of that effort, constantly says at her meetings "We never knew what we didn't know." If I can give two anecdotes, Neurontin was a medicine that was used for chronic pain in adults. We started to use it for chronic pain in children. It was abandoned, because it didn't work. And then the company came and did a trial under BPCA, and the dose was 40 percent too low. The dose in children had to be raised to 40 percent. It was equally effective, but we were using the wrong dose.

There's an anaesthetic we were using to sedate people in the ICUs for years and years. A new anaesthetic came out. It was much easier to use, but when they actually studied it versus the old anaesthetic, when they were trying to get labeling for it for pediatrics, the all-cause mortality of the new, easier-to-use and supposedly safer, was twice as high as the old regime.

So we don't know what we don't know until we look to see what we can find.

DR. GUTMANN: Just let me follow up, because regardless of whether you're recommending yes or no to this, everybody seems to agree that the line pre-threat, actual threat, is between immunogenicity studies and safety studies.

Why draw the line there, since that is limited information? It's better than none, but it's not as good as having the safety information. So I want to know what leads you to draw the line there, since it's not knowledge. Because you would have more knowledge, it's got to be some other barrier. What's the barrier to your recommending that we recommend not just the first stage, but safety studies?

DR. BERKELMAN: I actually would put forward that we are studying safety when we do the immunogenicity studies, and what I am aware of is that some people have put forward the idea of testing 70,000 children for safety, to make sure there's no rare adverse effect.

And so my sense of this is not that it's just so divided between the two, but you're trying to make sure that there's not a very common adverse event. And others may want to approach this differently, but I'm just thinking that I wouldn't want to see 70,000 children to look at this.

DR. GUTMANN: So, how many? What I'm trying to figure out is where you're -- and it's always difficult to be precise in drawing a line, so I'm not saying -- you know, we agree with you. But I want to know, is it because we really don't know how probable an anthrax attack is that you're recommending the smallest possible study, so we have some limited information? Or is it because you don't want to impose more risks on children, and so you want to keep the number of children small. I really don't understand why you're stopping with the first stage studies.

DR. BERKELMAN: There's one extra issue here, and that's that you can get safety data fairly quickly during the event. And you won't immunize -- you wouldn't vaccinate every child at once. Others may want to expand on that. What the magic number is for when you don't know it's a common

event, I don't have the answer. But I do think the immunogenicity, clearly that data you cannot get easily during the event. The safety data you can get more easily and more rapidly.

DR. RESNIK: Even though I said no at this time, it's based on the lack of evidence for the social benefit. For me, if there actually was an attack, or maybe if I were more privy to more information from intelligence sources, it would shift my reasoning towards saying yes to doing these studies. My no is really based on that there's just so little evidence in my book that this would really be worth it.

DR. GUTMANN: I understand that. Yes, Dr. Halsey?

DR. HALSEY: Let me clarify my answer, because I may have created some of your uncertainty. The answer to each of the questions that you posed, if you can remember them, is yes. It's all of those factors.

DR. GUTMANN: Okay. I can remember.

DR. HALSEY: I do believe it is justifiable to study small numbers of children to make sure that the product, at least, induces an immune response, and you get the right dose. And therefore, it's reasonable to expose relatively small numbers of children. I don't believe it's justifiable to expose 70,000 children. You know, the potential for the risk is not that great.

And so we can make decisions like that for each of the agents. If I thought the potential for risk, there was a yearly exposure, somebody releasing anthrax all the time, so it looked like it was going to be used on a regular basis, it would change my answer.

DR. GUTMANN: That's what I wanted to know. Anita, are you off the list now? Your hand was up next in line.

DR. ALLEN: Yes. Let me just ask a question about the combination of using the antibiotics -- I spoke to you about this during the break -- using antibiotics and giving the anthrax vaccine on a trial basis, in light of what was just said about doing a safety study.

Would it complicate what you learn from the study about safety if you were also giving the children antibiotics simultaneously?

DR. HALSEY: No, not for this vaccine. That doesn't necessarily apply to every potential one, but it would not complicate what you would learn if you were giving antibiotics simultaneously. And let me just clarify, during the anthrax exposures that took place, at the time people didn't know how long you needed to treat people with antibiotics. So they went 30 days, 60 days. People were uncertain, because the antibiotics do not necessarily eliminate all of the spores from the body, and you could then have disease occurring later. There were animal studies to show that.

So the thought at the time was that if we had the vaccine, if somebody were exposed, you would not just give the antibiotics, but then you would also start the vaccine, so that eventually you could stop the antibiotics.

Now, I think we learned -- and I would defer to others -- that, in fact, people who did stop the antibiotics after 30 days or so, there were no resurgent cases based upon the exposures that took place. But the simple answer to your question is no, it wouldn't complicate it. You could study both.

DR. ALLEN: And I had a second part question for two of the panelists who said or hinted that military children might be a good source of subjects for enrollment. I just want to raise some ethical questions about the justice of that particular viewpoint.

I mean, military families are subject to extraordinary pressures to both obey and to conform. Military families are disproportionately exposed to the need to sacrifice. Military children are

disproportionately dislocated and separated from their families. Military families are disproportionately African-American. Military families are disproportionately from the South.

I mean, I just think it's a really big deal to let the fact that, maybe, more military personnel have had the vaccine than others cause us to sort of say "Well, of course, obviously that's where we should go to find the children to enroll in the research." I just wonder whether you think that, in light of what I just said, maybe military families aren't the best place to go to find subjects for the experimentation.

DR. MOORE: Thank you for that. My viewpoint about this was not -- obviously, I hadn't considered that, not to prey upon a particular element of society. What I'm trying to say is that -- really, the ethicists will decide on whether that's an appropriate clinical trial to do.

My only belief was, if you have a set of people who have received the vaccine and believe in its safety and immunogenicity -- that is, who can testify, as opposed to many other groups who believe it is not safe, despite the lack of evidence supporting that -- it may be easier to recruit individuals, the children of those individuals. That is not to say that the parents of those children should feel compelled to do so, by any means. It's just an opportunity. In terms of recruiting patients for this sort of clinical study, when there is no actual threat, it makes it difficult to recruit for that study. And I offer only one possible group to enroll.

DR. WENDLER: I was just going to say that I had your concerns about the recruitment side of it, and I think what we tend to do is, it's good to use experienced people in this way when you think that experience gives them greater understanding or insight into the study.

So we do pain studies at our institute, and people who have had the pain experience, we think they probably understand the risks better than people who haven't had those. But I think in this case, it's not clear to me that having had the vaccine really necessarily correlates with you having any deeper

understanding of the risks, the potential benefit, than somebody who hasn't undergone it. So I'm not sure either.

DR. GUTMANN: Thank you. Nelson?

DR. MICHAEL: So it's pretty obvious considering how I'm dressed today that I couldn't pick up on that point. Well, really, Anita is going to make my job a whole heck of a lot easier, because she raised all the issues. I mean, military personnel, both those who wear my uniform or those that wear the uniform of our sisters and brothers around the world are considered a vulnerable research population, end of discussion. And the Department of Defense IRB has taken extremely conservative view in terms of research volunteers, even in Army studies, that are active duty or reservists, for exactly those reasons.

That said, I don't think it would be ethically intrinsically wrong for military members to be included in these kinds of studies if they chose to, but I would imagine that that would be done in the context of studies where there would be a broad recruitment effort. And you might have better uptake in military families, just because military families in general tend to be goal-oriented, and you get some of the other spirit of volunteerism that accrues in those populations.

But I do think that everything Anita said needed to be said, and I thank her for saying it.

DR. GUTMANN: Alex?

DR. GARZA: Thank you. As an Army reservist, and having received both the anthrax and the smallpox vaccine, and still being able to chew gum and walk at the same time, I'm a testament to vaccine production.

Anyway, I wanted to make sure -- this is more of a comment, and I would be interested in your thoughts on it. We've talked a lot about safety and efficacy of the vaccine, and there seems to be some interplay on risk involving vaccine.

But I think when we're talking about risk, we talk about two separate risk worlds. And I've heard people talk about vaccine development for influenza, as opposed to vaccine development for anthrax, and I think those are two distinctly different risk categories, as I think you understand.

But the thing is that influenza comes every year. We know a lot about influenza. We know a lot about influenza vaccine. We know a lot about side effects of developing vaccines. We know a lot about the influenza virus. We don't know a whole lot about anthrax. So it's one of those known unknowns, as former Secretary Rumsfeld would say. Influenza, known known. Anthrax, known unknown.

And then I would go a step further, and say intelligence data, a lot of unknown unknowns. So for those of us who work in the intelligence world, there is no such thing as perfect intelligence. None. We work a lot on what we can get in bits and pieces. We try and put stories together. Not stories, but we try and put plausible scenarios together, and we try and figure out risk to the nation. And then we take that, and we apply it to how we operationalize.

And so I would just caution people to not place these sorts of scenarios into a very typical risk paradigm, where we have a lot of data from past experiences, because I think we run into a fallacy by trying to project that onto a very unknown situation, but a plausible, with some, not zero, risk. That's all I wanted to say.

DR. GUTMANN: John?

DR. ARRAS: Two issues I want to raise. With regard to subject selection, I take all these excellent points about the vulnerability of military, but I'm reminded in this context of Hans Jonas's famous article, going back to the 1970s, where he argued that research subjects should ideally come from those populations that are most knowledgeable and most identified with or enthusiastic about the medical mission. So if we went with that sort of criterion, which may not be a great criterion for garden-variety

research, but in this kind of case it might actually be a good criterion. In which case, we might want to look for volunteers from places like the CDC, the NIH, Fort Detrick, and other places of that sort. So if you have any comments on that, let me know.

The second thing that I would like to get your help with is the question of the likely risks posed by the anthrax vaccine. Sitting here the last day or so and reading this literature, I'm feeling like a pinball, just being whacked around, and changing my mind with every other article that I read, based on the facts that are alleged there.

So here's a snippet from a paper published in MMWR, that our staff provided for us. This is from the ACIP committee of CDC, looking at voluntarily reported events, adverse events, to the CDC, between the years 1998 and 2008. So these are not percentages relating to everybody who got this vaccine in the military. The percentages relate to those who self-reported an adverse event. But I still want to get your take on how we should interpret this, okay?

Pain: 13%

Pain, tenderness and swelling at the site of the immunization: 10%

Rash: 10%

Headache: 16%

Now, all of that might allow us to lump these risks under the category that I wanted to call a minor increase over a minor increase of minimal risk. The final line really caught my attention:

Serious adverse events: 9.9%, including hospitalization, disability, and/or death.

So, what does this mean?

DR. HALSEY: I deal with such data on a daily basis, basically. And I think I know the article. I know the ACIP recommendations on this. That's an uncontrolled, no comparison group, reports of

events that have occurred, and you didn't state the time interval after vaccine that's there, but commonly 30 days would be something I might assume. But it might be there in the title of that.

So that there's not evidence of a causal relationship with any of the things you put there, with the possible exception of the local reactions and the pain at the site of the injection. And so if we took all of us sitting around the table and we amplified this 20 times, and then we measured the potential for an adverse event of any kind, there would be a lot of headache, muscle pain, joint pain, other --

DR. GUTMANN: Not as a consequence of this conference, I hope.

(Laughter.)

DR. HALSEY: There would be hospitalizations of some rate. And so that's taking everything that happens to those people, and you have to interpret it that way, okay? And so one of the most difficult things we have to face in the studies of vaccine safety is public misunderstanding of causal relationships. And I would just make that point, that other than the pain and the local reactions, I can't say what the evidence is for an increased risk from those data. We'd have to poll the controlled trials where you had a comparison group who received a placebo, or didn't get a vaccine but didn't know whether they did or not, to see whether there's an increased rate of those events.

DR. GUTMANN: Very helpful. Thank you. Dan?

DR. SULMASY: Thanks. I wanted to bring us back to another task for the Commission, which is creating the ethical framework for evaluating these sorts of studies, and to particularly ask David Wendler, who artfully dodged the other question, so we'll put you on the hotseat with this one, whether or not the sort of schema that you were laying out for us depends on a particular view of the common good.

A sort of liberal sense, which I think is where most of us come from, might say that the common good is simply those factors that contribute to our individual flourishing. A utilitarian view might be that it's just the sum of all the goods that are created by this. But when you started talking about a contributive good, it seems to imply a communitarian or sense of solidarity in which my individual good is, in part, constituted by the good of the whole.

And if we're going to allow parents to volunteer their children in this kind of a study, it seems to me that we're allowing them to say that their children can be educated in such a way, and brought up in such a way, that they have this kind of an understanding of the common good. Is that sort of framework or understanding of the common good necessary in order to justify this kind of a study?

DR. WENDLER: I've spent a lot of time looking at different justifications for doing what I call non-beneficial pediatric research, and I haven't found one that I think is otherwise convincing, other than the one that I've tried to describe and I've tried to defend.

So I think that, if you don't agree with that view, then I think you should be extraordinarily cautious about saying that this type of research is acceptable, because you, as far as I can tell, don't have a good explanation for why you think that's the case.

With that said, I think this is a good justification. So, what does it depend on? I don't think it depends on having a particular political view, say being a communitarian or something like that. But what it does depend on, it depends upon a particular objective account of what makes our lives go better and what makes our lives go worse.

And we could obviously talk about that a lot. Most of the people that I have ever talked to about this, I think they agree with the basic intuitions, that there are certain ways in which your life goes better and certain ways in which your life goes worse.

So I think you need to assume that for this account to go. So if you were purely a subjectivist about individual interests, that it's completely up to what you care about that determines what's in your interest, then this argument would work only if you had reason to predict that the kid you were enrolling was going to grow up to have the kinds of preferences and values that led for this to be a benefit. Now, you might be able to do that, but it would be more complicated.

DR. GUTMANN: David, could I just follow up in the spirit of Dan's question and your answer? You said something in response to my earlier question that I think provides a, compatible to what you've just said, extension of an answer to Dan, which is if it is the case that, in the normal course of daily life of children, there are examples of where parents and children not only consent to do things that modestly increase their physical risks for a public good -- like building houses in Habitat for Humanity, and risking nailing a nail in their finger, or putting themselves at greater risk -- that would give some factual evidence that the actual lives that not all, but many, children and their parents live make room for this idea that there are goods that don't accrue directly to yourself, but that increase your sense of worth of life by contributing to a larger public good.

It doesn't solve all of our problems about what level of risk and so on, but it opens the door, without having a thorough-going communitarian view of life, to saying that even people who most of the time live their lives in ways that they will put themselves at risk only for themselves or their immediate family, some also do these other things which aren't too high a risk.

Because I think the higher the risk you get, the more we should worry about recommending subjecting children who are not directly benefitting from it, for the reason I gave at the extreme of the child soldier.

DR. WENDLER: Absolutely. I think that's well said, and I think it's basically two different ways you could try to make this same argument. One, I was trying to run with Dan as sort of a substantive argument about the justification.

I think another way you could do it is just basically by analogy, in effect. You say "This activity that we're allowing here is similar to these other contexts in which we allow children to face risks for the benefit of others. Everybody thinks it's acceptable as long as we think the risks aren't very different and they're sufficiently analogous." It seems like we're being at least consistent, and that gives us some support.

Some people might then question why those are okay, but --

DR. GUTMANN: Could I ask something in the spirit of -- Dan, did you want to follow up?

DR. SULMASY: Yes, just to say, again, if you're to run in the objective list sort of account of the good, as you were suggesting, then at least part of that objective list has to include something of contribution to the common good, some sort of interpersonal good, which is part of your own good.

DR. WENDLER: Right.

DR. SULMASY: So it doesn't have to be in that sense, then, a full-blown communitarianism, if you have contribution to the social good as being part of your own flourishing as an individual, as part of your objective list.

DR. WENDLER: And I'll just say really quickly, I think basically the way it works on my view is that I think that we have lots of different interests, and lots of ways in which our lives can flourish or not flourish. I think one of the interests we have is, basically, we have an interest in living a better overall life. That's a good thing for us, to have lived such a life.

So then basically what you need is, you need an analysis of what constitutes a better and worse life in that way, and you could make good arguments that doing things that, all else being equal, cause serious harm to other people, makes your life, for you, go less well. And by reverse, doing things that dramatically improve other people's lives will make your life go better for you.

But yes, that's the claim you have to make.

DR. GUTMANN: I have a different question. We haven't discussed the factor which we did, in an earlier report, recommend, and it happens to be a part of vaccine research, but not a part of other research in this country, which is compensation for harm.

Am I right or wrong to feel some ethical assurance that, in the case of testing vaccines on children, which are not of direct benefit to them, if they are harmed, there would be recourse to compensation? And if there wouldn't be, should we be recommending, in this case, as we have in our previous report with regard to adults -- should we be recommending that, were the government to conduct a study that subjects children who are not directly benefitting to risks, that there be compensation for harm?

DR. GORMAN: There is a mechanism, and it could be expanded to include anthrax. There is the PREP Act -- and I forget what PREP stands for, but someone will fill you in afterwards -- which allows individuals to petition the government for compensation for vaccine or therapeutic measures for declared public health emergencies or biodefense testing. So the clinical studies done for the H1N1 vaccine were done under this act.

DR. GUTMANN: Dr. Berkelman, I'd like to know your view on the ethicals, what you think of the ethics of such a recommendation.

DR. BERKELMAN: I would agree with compensating in this case. I mean, really, I agree with this.

DR. GUTMANN: Would anyone argue against a recommendation that, in cases like this, there ought to be compensation in the case of harm?

DR. WENDLER: I don't think anybody would. I think it's a great idea. I think there are lots of different people and groups over the years who have looked at this, and they all come to that recommendation. The extent to which it actually gets realized, I think, is a little bit, unfortunately, less clear. It should be there. Whether or not it would be, I think would depend.

DR. GUTMANN: I think, Dr. Gorman, if you could point to how it not just should, but how you think it can actually be realized, that would be helpful for us in our deliberations.

DR. GORMAN: I'm not sure what you're talking to.

DR. GUTMANN: The PREP Act, how it actually, practically speaking -- since compensation is not now available generally for research harms, in this particular case it seems particularly important, for the reasons that I outlined. How, practically speaking, might this be carried out?

DR. GORMAN: I am not an expert on the PREP Act, but my understanding is that the Secretary makes a recommendation to some body of people, which then gets written into the PREP Act law, and it has a start date and an expiration date. And during that time, if it's an emergency, how long they consider the emergency, the PREP Act protects manufacturers and researchers and other people delivering the countermeasures from people being able to sue them, but it does give the advantage for them -- I don't think they use the word sue, but petition the government for compensation for harms that occur during the trial.

DR. GUTMANN: Dr. Resnik?

DR. RESNIK: I happen to be working on a research project right now in which we're looking at compensation policies, and petitioning for harm is not an adequate way of compensating people, because you have to get an attorney and everything, and you may not be able to.

I would recommend that -- I mean, it depends on who the sponsor and the institution is, because these policies vary. But there are some institutions and some sponsors that have compensation for injury policies, and they don't require you to get an attorney. You just have to work with the policy.

I would suggest, potentially as a first step before we have to make something national policy, is for any funding mechanism to identify institutions and sponsors that would be potential candidates, that already have compensation policies in place that would be adequate for doing this kind of research.

DR. GUTMANN: Are there any questions from members of the audience?

DR. KRUG: Thank you for asking. I'm Dr. Steve Krug, and I'm the chair of the Disaster Preparedness Advisory Council of the American Academy of Pediatrics. This has been a great discussion on a thorny issue, and I thank you for considering this.

I participated on the anthrax -- I was not a member of the working group, but in their deliberations, and many of the same issues came out. I can't answer some of the questions, but I would ask the very knowledgeable people who are at the table to maybe discuss in greater detail about the reality of what would happen tomorrow.

A city gets dusted, and the CDC will recommend that we give vaccine and antimicrobials to everybody. The adult patients will get those medications without any investigational protocols attached to them. The children, however, in theory -- maybe I won't choose to do this in my institution, but I would have to, actually, I believe, get consent from every single family member of every single child, parents, in order to

administer vaccine and, arguably, the antimicrobials as well, because they would be distributed under an IND protocol. These guys know a lot more about that than I do.

Question one: how does one actually get truly unbiased, informed, non-pressured consent in the midst of a health emergency where I'm telling you about something that could be dangerous, and yet I'm also sort of hanging over your head, going "By the way, your child may die"?

Secondly, what's the realistic sort of barrier to actually, I've got to immunize 10,000 people in my emergency department tomorrow, yet it's going to take me three to four times the amount of time to immunize every single child, because I have to go through this consent process? Because that's what I should do, and I should inform everybody, but don't need to do that for adults. So does that create a real problem for the kids?

DR. GUTMANN: Thank you. This is going to be our final question, so anyone who would like to answer, I welcome the answer. Dr. Wendler?

DR. WENDLER: It's a good question. I think part of it depends upon -- if you're saying it's going to be difficult once you have an event to get consent, it seems to me that the kind of study you'd be doing then and the concerns you'd have would be very different than doing a study pre-event.

So I assume if you're just giving it to kids post-event, then that's because you assume that it's in their interests to get it. And if that's right, then I think you have -- still, you want to make sure people understand, and you want to get their consent, but I think that the standards and the demands for getting consent in that context would be very different than one where you're just giving it for somebody pre-event, just to find out what the immunogenicity is or the risks are.

DR. GUTMANN: Dr. Gorman and then Dr. Halsey.

DR. GORMAN: At the present time, the statutes do not allow for any loosening of those constraints, so there would be consent. Under 407, it would be two parents' signatures, so you have a first responder who has been called away, is staying in the fire station for 36 hours, during which time his child can't be vaccinated because they're at the fire station. Or the nurse who's at the hospital. It poses enormous logistical constraints.

I agree completely with Skip Nelson. When you have the parent, the paper, and the child all there together, you're talking about an extra minute. An extra minute times 80,000 or 10,000 adds up to a lot of minutes. But getting the child, the parent, and the paper all in the same place is a potential logistical nightmare.

DR. GUTMANN: Dr. Halsey?

DR. HALSEY: I would make several points. One is that I agree with Dr. Gorman that the regulations now to release the vaccine for use in children would have to be under an emergency use authorization from the FDA, which would require a consent process, which, having seen some of those for things that people had to develop even hurriedly, took more than a minute to do, and it's not something that would be done. It's more something like 30 minutes to really do it right.

But that's part of going back to one of the earlier recommendations, that there needs to be emergency planning for protocols that could be implemented in a situation like this, with less than one minute of a consent process. So that's got to be simplified. I think it changes -- it won't be under 407, because if there is an event, there is an exposure, there is potential real benefit to the child. So it changes it to 405, and it could be done very rapidly. So one of your recommendations should be the development of scenarios and protocols for each of these.

DR. GUTMANN: And so that -- go ahead.

DR. WENDLER: So if you think there's prospective benefit, it could be 405. The other thing is, it sounds like this probably could be reconstrued as research in emergency settings. So there are separate regulations for that.

DR. GUTMANN: Correct.

DR. WENDLER: And there are ways to do it. So for one, you could regard it as you're just going to give it for their benefit, and then later on do the research when you have time. So I think that's what you should do. You need to plan for it.

DR. GUTMANN: But it does underline Dr. Halsey's recommendation of having a protocol ahead of time, and needing a plan.

This has been enormously helpful. On behalf of everybody on this Commission, let us all thank our panelists. Really terrific.

(Applause.)

DR. GUTMANN: We have our work cut out for us. But before we adjourn, I'm going to turn this table over to our vice chair for some closing comments.

DR. WAGNER: I have very little to add, but I bet I speak for a number of us. In the spirit of those that say "To be educated is not necessarily to know the answers, but to have a better handle on the questions," I feel better educated. I wish I also knew more of the answers.

But quite seriously, owing to the kind of testimony that you've given us and what we've heard today, and some of the debate that we have been able to have as well, I do feel as though we are zeroing in on the right sets of questions that can help us, that can lead us to what I think will be a reasonable, well-received, and very helpful recommendation for the public.

So again, with thanks to all of you and thanks to my fellow commissioners, we've got more work to do.

DR. GUTMANN: Thanks to fellow commissioners, and thanks to the public for a terrific set of questions, including the last one. So thanks, everybody, and we will convene again in November, in Chicago.

(Whereupon, the above-entitled meeting was concluded at 3:44 p.m.)